Synapses

Introduction

Action potentials are propagated from one cell to another—one cell communicates the signal and the other receives. However, if a signal simply jumped from one cell to the next, it would have to cross two cell membranes and a small distance between. This "small distance" would cause a substantial drop (a degradation) of nearly 4–5 orders of magnitude, which would fail to produce the action potential on the receiving cell. To get around this, cells have two major forms of communicating that action potential: electrical gap junctions and chemical neurotransmission.

Gap Junctions

Gap junctions are tiny pores in neighboring cells connecting the two cells physically. These junctions are formed by **two connexons**, one on each cell, each connexon made up of **six connexins**. The cytoplasms are as one—the connexons align and allow the passage of electrical signals, water, and small ions. Gap junctions allow passage of signal in **both directions**, and directionality is conferred based on refractory periods. **Rectifying gap junctions** are special gap junctions that ensure unidirectionality. Gap junctions confer electrical transmission between **cardiac myocytes**. Gap junctions are also used to connect cells of an epithelium.

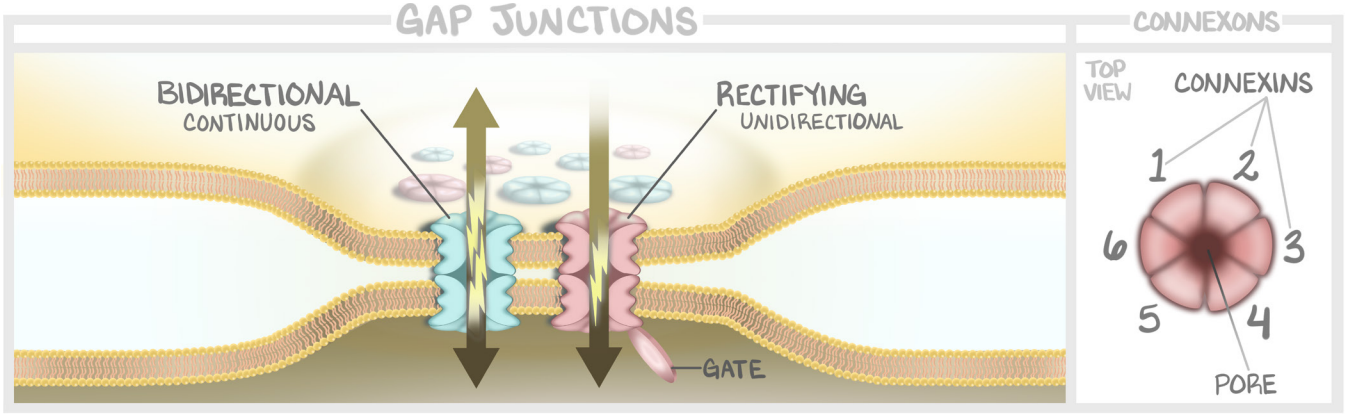

Figure 8.1: Gap Junctions
Gap junctions connect two cells that are closely opposed to one another. The six connexins make one connexon. Each cell has a connexon. The connexons align. The cytoplasm becomes effectively contiguous and electrical depolarizations of one cell's membrane can propagate through the gap junction and onto the membrane of the next cell.

Chemical Transmission

Neurons use **chemical transmission** at the **synaptic cleft**, where molecules move across the cleft from presynaptic neuron to postsynaptic cell receptors. The **presynaptic cell** is carrying the signal as a propagating action potential down the axon. The axon terminates at the synaptic cleft, where the presynaptic neuron has stored a large density of highly localized neurotransmitter. The **postsynaptic cell** receives the signal from the presynaptic cell by way of receptor activation. The postsynaptic cell has a high density of neurotransmitter receptors also located at the synaptic cleft. The electrical signal from the presynaptic neuron is translated to release of neurotransmitter; that chemical crosses the synaptic cleft and binds to the receptors on the postsynaptic cell, which regenerates the electical signal on the postsynaptic cell. Of course, as we will see, medicine can never be that easy.

In addition to ionotropic effects (hyperpolarization/depolarization), it is possible to have metabotropic effects as well. Follow along with Figure 8.2.

1. Vesicles are created and packed with large peptide neurotransmitters, then trafficked to the presynaptic terminal along microtubules. The vesicles are parked at the distal end of the presynaptic cell terminal and remain while the cell membrane is at rest.
2. An action potential arrives, propagated by myelin sheaths and nodes of Ranvier.
3. The action potential depolarizes the presynaptic membrane terminal, activating voltage-gated calcium channels.
4. Calcium influx induces fusion of the vesicles and subsequent exocytosis of the neurotransmitter.
5. The neurotransmitter binds to receptors on the postsynaptic cell, activating them.
6. The neurotransmitter is either reuptaken or degraded by enzymes in extracellular space.

Receptors can be metabotropic or ionotropic. **Ionotropic** means that the binding of the ligand to the receptor directly opens an ion channel. **Metabotropic** receptors bind neurotransmitter ligand and induce cytoplasmic changes that result in the activation of second messengers.

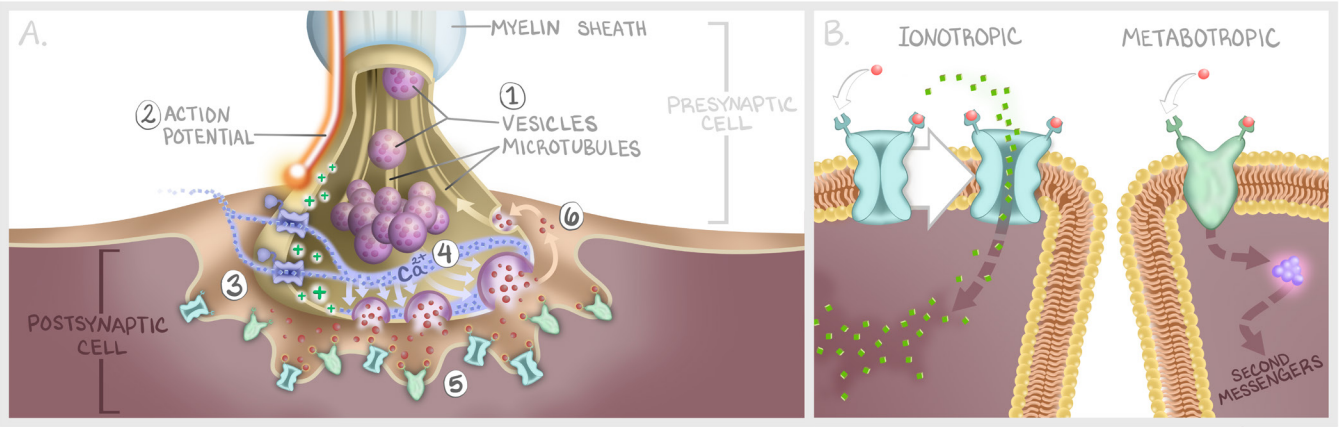

Figure 8.2: Synaptic Cleft
(a) The presynaptic neuron process of neurotransmitter synthesis, release, metabolism, and reuptake is demonstrated corresponding to the numbers above. (b) The postsynaptic response is either ionotropic or metabotropic, as discussed in the next section.

Skeletal muscle uses the ionotropic nicotinic acetylcholine receptor at the motor endplate, the synaptic cleft between the motor neuron and the muscle it innervates. This channel is permeable to **both Na^+ and K^+**. When **activated** by acetylcholine, the channel opens. Because Na^+ and K^+ ions are exchanged equally, the membrane potential is sent between the two ions' Nernst potentials (Na^+ +65, K^+ −90) somewhere in the −30 to −10 mV range (all of which is above the threshold potential of −60). When not activated by ligand, gates are closed, and no ions flow.

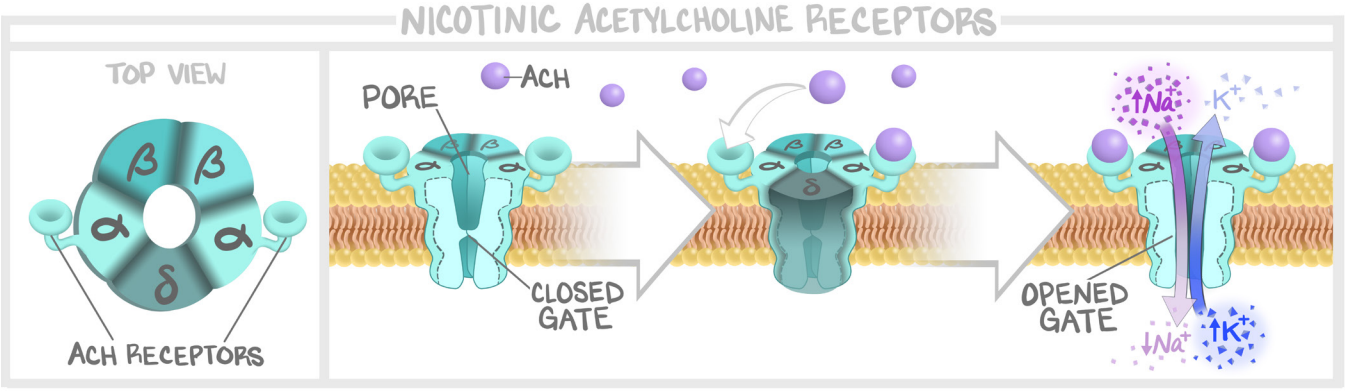

Figure 8.3: Nicotinic AChR
The channel is a heteromeric pentamer (five subunits of different types) consisting of one δ, two α, and two β subunits. There are four transmembrane domains. The receptor becomes activated when two acetylcholine ligand molecules bind, each ligand to its own α subunit. When activated, the gate to the pore made by the α subunits opens. Both Na^+ and K^+ flow down their concentration gradients, depolarizing the postsynaptic membrane.

Postsynaptic Potentials

An **Excitatory Postsynaptic Potential** (EPSP) is a response of the postsynaptic cell membrane that increases the likelihood that the cell will reach threshold. It's defined by any depolarizing stimulus, usually mitigated by **Na^+ conductance**. Though there are variations, such as those mitigated by **Ca^{++} conductance**, focus on the association with Na^+ and EPSP.

An **Inhibitory Postsynaptic Potential** (IPSP) is any response of the postsynaptic cell membrane that prevents the postsynaptic cell from depolarizing to threshold. IPSPs are **hyperpolarizing** signals often mitigated by **K^+ conductance** or **Cl^- conductance**. There are many variations that can be an IPSP, but associate K^+ with IPSP.

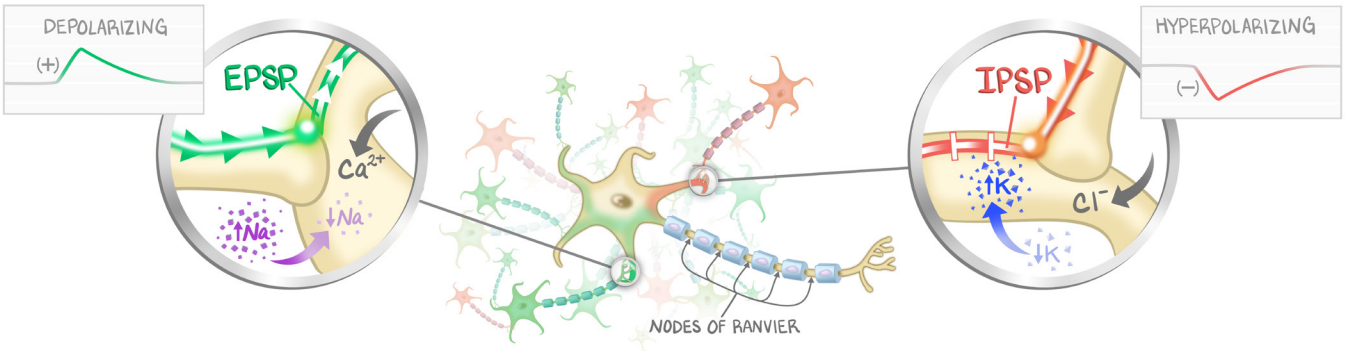

Figure 8.4: EPSP and IPSP
Excitatory postsynaptic potentials are depolarizing, often secondary to increased Na^+ conductance. Inhibitory postsynaptic potentials are hyperpolarizing, often secondary to Cl^- or K^+ conductance. Neurons have many simultaneous inputs, both EPSPs and IPSPs. Only when enough EPSPs summate will the neuron depolarize.

Whether EPSP or IPSP, these potentials are **singular** and **graded**. That is, the depolarizing or hyperpolarizing effect is felt locally where the channel is present, and the signal decays over time and space. This is how neurons accept thousands of inputs from other neurons and come up with one common decision—fire or don't fire. One EPSP will not depolarize to threshold. One IPSP could not prevent a depolarization. But when there are multiple channels, each offering "one unit" of EPSP or IPSP, these all contribute to the overall voltage which then may be sufficient to make a difference. This is known as summation.

Summation

There is both **spatial summation** and **temporal summation**.

Spatial summation. Imagine a neuron with a hundred inputs. Fifty are EPSP, fifty are IPSP. A single EPSP is insufficient to reach threshold. And imagine that each EPSP is as depolarizing as each IPSP is hyperpolarizing. If all fifty EPSPs fired simultaneously without any IPSPs, those fifty EPSPs would **add to each other.** While no one EPSP was sufficient to reach threshold, with all fifty acting at once the combined effect is sufficient to reach threshold. This multiple-inputs-to-one-postsynaptic-neuron is how our CNS actually works. A balance of EPSPs and IPSPs, thousands of simultaneous inputs waiting for a tip in the balance. Spatial summation is the net combination of EPSPs and IPSPs at a given moment. The motor endplate uses spatial summation in a positive way—so many nicotinic acetylcholine receptors depolarize in such a condensed space, it guarantees that one motor neuron's firing will result in depolarization of the skeletal muscle.

Temporal summation. Because the depolarization of the postsynaptic cell lasts longer than it takes for the channels to close, another stimulus of the same input can produce additional depolarization. The first signal gets the postsynaptic cell from –80 to –75. As that graded EPSP is decaying to –78, the same neuron fires again, depolarizing the post synaptic cell from –78 to –73. Repeated stimulation before the EPSP has decayed to resting potential is called **temporal summation**. Theoretically, one subthreshold input, if fired frequently enough, could reach postsynaptic threshold.

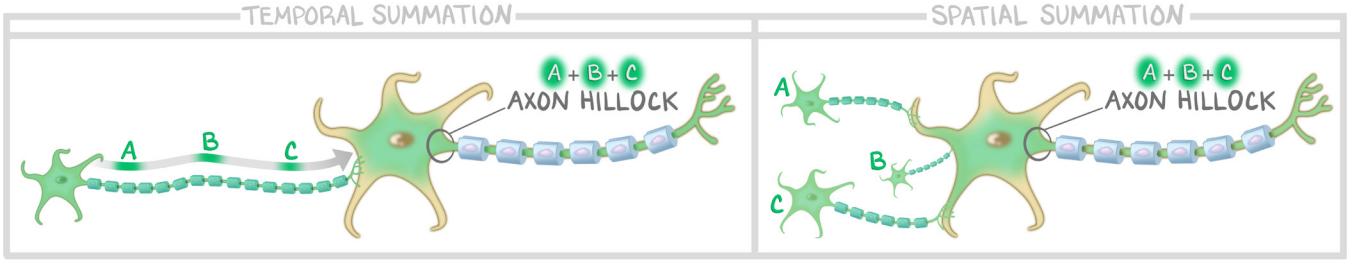

Figure 8.5: Summation
Spatial summation occurs when excitatory potentials from many different presynaptic neurons in proximity cause the postsynaptic neuron to reach its threshold and fire. Temporal summation occurs when a single presynaptic neuron fires many times in succession, causing the postsynaptic neuron to reach its threshold and fire.

Endplate Potential and Quanta, Calcium

A muscle fiber (a skeletal muscle cell) is innervated by only one motor neuron. One neuron may innervate many muscle fibers. The combination of one motor neuron and all the muscle fibers it innervates is called a motor unit. This is very different than neurons in the brain, where one neuron may have hundreds of inputs. There, the combination of hundreds of EPSPs and IPSPs decide whether that postsynaptic neuron depolarizes or not. In the motor unit there are no competing EPSPs and IPSPs. It's simply, "fire neuron, fire all the fibers in the motor unit." But we now know that "fire neuron" actually means, "release many neurotransmitters that all have EPSP effects and that summate on the postsynaptic muscle." This is because the action potential of the presynaptic neuron releases so many vesicles at once that it guarantees postsynaptic depolarization. Here's how we found out.

If we poison a muscle with curare, voltage-gated sodium channels are permanently blocked—no action potentials. No firing of the neuron, no firing of the muscle. But by reading the voltage of the muscle, we are able to detect a change in the membrane voltage. These changes happened infrequently, but each one was the same. It had the same amplitude and same graded dissipation. But no muscle fired. Something other than the depolarization of the presynaptic neuron leads to the depolarization of the muscle. This

seems trivial now, as we know that neurotransmitters are **packaged in vesicles** and released as **quantal packets**—one vesicle fusion = one vesicle's worth of neurotransmitter = one voltage change. The action potential of the presynaptic neuron could not be generated, but spontaneous release of neurotransmitter, just one quantum, happens without the action potential.

If we poison a muscle with curare, but then inflict a depolarization to the membrane experimentally, we could get the same response. Depolarization of the presynaptic membrane did result in depolarization of the muscle. What we found is that **one vesicle** released results in a reproducible EPSP on the motor endplate, called an **endplate potential** (EPP). The EPP was the voltage tracing that resulted from one vesicle releasing one vesicle's worth of ACh. The EPP is the smallest unit of depolarization. And if we increased the voltage, we got more EPPs that stacked together. One vesicle's worth of neurotransmitter has a reproducible EPSP. One vesicle, one quantum of ACh, one unit of depolarization, or one EPP. Two vesicles, two quanta of ACh, two units of depolarizations, or two EPP.

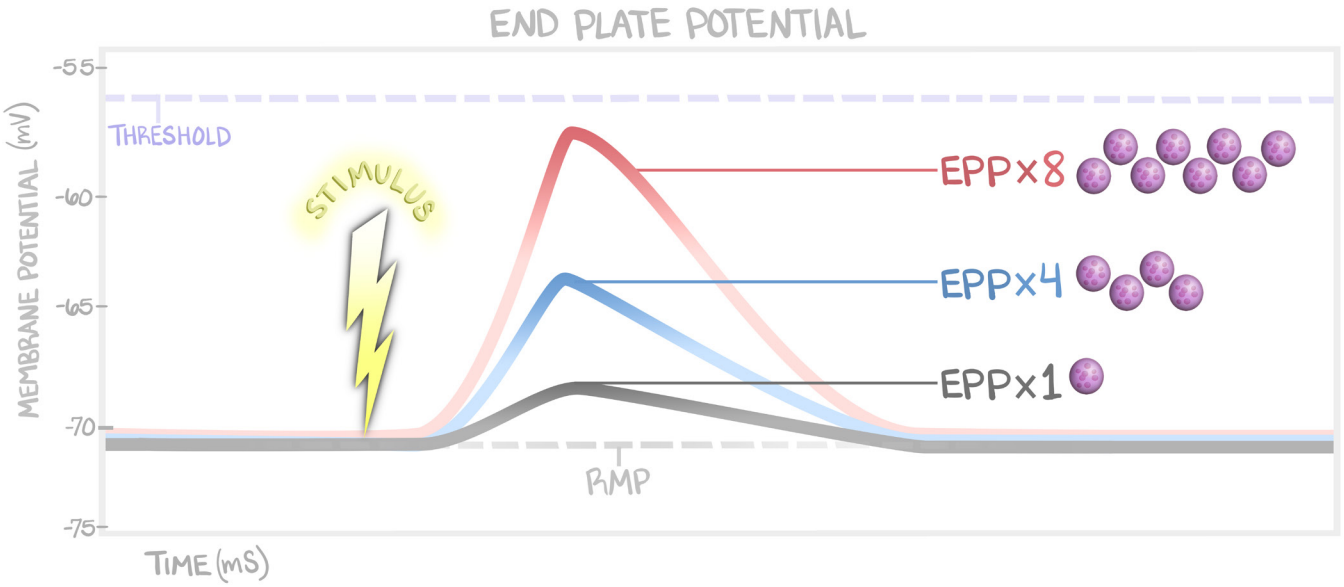

Figure 8.6: Quanta
Neurotransmitters are stored in vesicles. Vesicles contain "one unit" of presynaptic signal. The signal they induce in the postsynaptic cell is reproducible and graded, and can summate. The signal may be hyperpolarizing or depolarizing. At a synaptic cleft the vesicle must be released, the neurotransmitter must bind to the postsynaptic receptor, and the intended ionotropic receptor must open.

So we looked for something else. Throw away the curare! The Na^+ channels work. Presynaptic action potentials fly into the presynaptic terminal with ease. But block calcium channels, and no postsynaptic depolarization occurs. That's when we deduced **calcium influx** regulates **vesicle fusion**. It was the not the degree of depolarization of the presynaptic cell that mattered, it was that depolarization of the presynaptic cell led to a degree of calcium influx, which regulated how many vesicles fused, which in turn regulated how much neurotransmitter was released, which in turn determined how many receptors got activated, and how many EPPs were generated. Without poison or disease, the presynaptic motor neuron releases so many quanta of neurotransmitter that the skeletal muscle fiber always depolarizes.

But think of all the ways this system can break. And you better believe that diseases and drugs can affect this system. The action potential must arrive, calcium channels must open, vesicles need to fuse, neurotransmitter has to bind the receptor, and the receptor then needs to open. We tackle that in #10: *Neuromuscular Diseases*. But first we cover how cells are connected to each other in #9: *Epithelium*.